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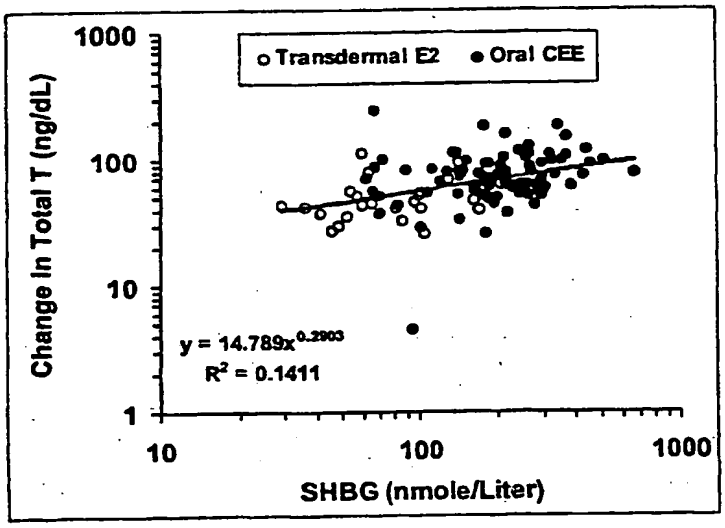
(54) Title: ADMINISTRATION OF NON-ORAL ANDROGENIC STEROIDS TO WOMEN



(57) Abstract: The present invention provides compositions, methods, and kits for improving health in a woman having elevated sex hormone binding globulin (SHBG) levels, or who is receiving oral estrogen supplementation, by non-orally administering an effective amount of an androgenic steroid. Further, the present invention provides compositions, methods and kits for coadministering an effective amount of an orally administered estrogen and an effective amount of a non-orally administered androgenic steroid for women in need of estrogen supplementation. Fig. 1 shows the change in total testoterone level versus baseline SHBG level during application of transdermal testoterone patch (300 mcg/day nominal delivery) to patients concomitantly receiving transdermal estradiol or oral conjugated equine estrogens. Fig. 2 shows the change in free testoterone level versus baseline SHBG level during application of transdermal testosterone patch (300 mcg/day nominal delivery) to patients concomitantly receiving transdermal estradiol or oral conjugated equine estrogens.

WO 00/76522 A1

ADMINISTRATION OF NON-ORAL ANDROGENIC STEROIDS TO WOMEN

RELATED APPLICATIONS

This application claims priority to United States Provisional Patent Applications Serial No: 60/138,851; Serial No: 60/138,854, and Serial No:60/139,323, each of which was filed on June 11, 1999. Each of these applications is hereby incorporated by reference.

THE FIELD OF THE INVENTION

This invention broadly relates to the administration of androgens to women. Accordingly, this invention covers the fields of pharmaceutical sciences and medicine.

BACKGROUND OF THE INVENTION

It is known that a functional level of androgenic hormones in females promotes sexual health and activity, feelings of well being, maximizes muscle mass and function, and inhibits bone loss. Further, a functional level of androgenic hormones may promote cardiovascular and coronary health, decrease breast tenderness, decrease vasomotor instability, modulate immune function, enhance certain cognitive abilities, improve urogential health, reduce estrogen supplementation related side effects, and provide direct neuroprotective effects.

The attainment of functional levels of androgenic hormones in women, such as testosterone, may be influenced by the serum concentrations of sex hormone binding globulin (SHBG). SHBG is a protein produced by the liver that binds sex hormones such as testosterone and estradiol in the blood. The SHBG-bound sex hormones are

ethylestrenol, oxandrolone, bolasterone and mesterolone, testosterone propionate, testosterone cypionate, testosterone phenylacetate, and testosterone enanthate, testosterone acetate, testosterone buciclate, testosterone heptanoate, testosterone decanoate, testosterone caprate, testosterone isocaprate, isomers and derivatives thereof, and a combination thereof.

The amount of androgenic steroid to be administered may be measured according to several different parameters. In one aspect, the amount of androgenic steroid administered may be an amount sufficient to achieve a therapeutic effect equivalent to a total testosterone serum level of from about 15 to about 1000 ng/dl. In another aspect of the present invention, the amount of androgenic steroid administered may be an amount sufficient to achieve a therapeutic effect equivalent to a free testosterone serum level of from about 0.5 to about 30 pg/ml. In a further aspect of the present invention, the amount of androgenic steroid administered may be an amount sufficient to achieve a therapeutic effect equivalent to a bioavailable testosterone serum level of from about 1 to about 70 ng/dl. In yet another aspect of the present invention, the amount of androgenic steroid administered may be an amount sufficient to achieve a therapeutic effect equivalent to a testosterone dosage of at least about 50 mcg/day.

Examples of specific estrogens which may be utilized in connection with the method of the present invention include but are not limited to: 17β-estradiol, 17α-estradiol, conjugated equine estrogen, esterified estrogen, micronized estradiol, sodium estrogen sulfate, ethinyl estradiol, estrone, tibolone, selective estrogen receptor modulators (SERM's), phytoestrogens, isomers and derivatives thereof, and a combination thereof. In one aspect of the invention, the amount of estrogen administered may be a dosage sufficient to achieve a therapeutic effect equivalent to a conjugated equine estrogen dosage of about 0.2 to about 3.0 mg/day.

Various forms of non-oral administration of androgen may be employed in accordance with the methods of the present invention, including but not limited to: topical administration, or parenteral administration, or a combination thereof. In one aspect, the forms of topical administration include without limitation, transdermal, or transmucosal, or sublingual, or a combination thereof. In another aspect, the

In describing and claiming the present invention, the following terminology will be used.

The singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a transdermal patch" includes reference to one or more of such transdermal patches, and reference to "an estrogen" includes reference to one or more of such estrogens.

"Sex hormone" refers to any hormone which affects the growth or function of the reproductive organs, or the development of secondary sex characteristics. In one aspect, sex hormones include, but are not limited to androgens, estrogens, progestins, and other hormones which are known in the art.

"Androgenic steroid," or "androgen," refer to a steroid, natural or synthetic, which exerts its biological or pharmacological action primarily by binding to androgen receptors. Examples include, but are not limited to: testosterone, methyltestosterone, androstenedione, adrenosterone, dehydroepiandrosterone, oxymetholone, fluoxymesterone, methandrostenolone, testolactone, pregnenolone, 17α-methylnortestosterone, norethandrolone, dihydrotestosterone, danazol, androsterone, nandrolone, stanozolol, ethylestrenol, oxandrolone, bolasterone, mesterolone, testosterone propionate, testosterone cypionate, testosterone phenylacetate, and testosterone enanthate, testosterone acetate, testosterone buciclate, testosterone heptanoate, testosterone decanoate, testosterone caprate, testosterone isocaprate, as well as esters, derivatives, prodrugs, and isomers thereof.

"Testosterone" refers to the compound having the IUPAC names (17β)-17-Hydroxyandrost-4-en-3-one, and Δ^4-androsten-17β–ol-3-one, as well as their isomers. Testosterone is listed in the Merck Index, entry no. 9322, at page 1569, 12th ed., (1996).

"Estrogen", and "estrogenic hormone" refer to any substance, natural or synthetic, that exerts a biological or pharmacological action primarily by binding to estrogen receptors. Examples include but are not limited to: 17-β-estradiol, 17-α-estradiol, estriol, estrone, and phytoestrogens. These estrogens may be derivatized or modified to form, for example, conjugated equine estrogens, esterified estrogens, ethinyl estradiol, etc. Examples of esterified estrogens include but are not limited to:

from Dunn et al., Transport of Steroid Hormones: Binding of 21 Endogenous Steroids to Both Testosterone-Binding Globulin and Corticosteroid-Binding Globulin in Human Plasma, *J. Clinical Endocrinology and Metabolism*, Vol. 53:58-67 (1981)). Represented binding affinity constants (K values) for particular sex hormones and SHBG are provided in Table 1 as follows. (adapted from Dunn et al. 1981)

Table 1

Sex Hormone	K (10^6 Liter/mole)
Androstanediol	1300
Androstenediol	1500
Androstenedione	29
Androsterone	14
Dehydroepiandrosterone	66
Dihydrotestosterone	5500
Estradiol	680
Estriol	4.3
Estrone	150
Progesterone	8.8
17-hydroxyprogesterone	9.9
Testosterone	1600

For the purposes of this application, SHBG binding affinity constants exceeding about $1x10^6$ Liter/mole indicate high affinity binding.

The structure and proposed functions of SHBG have been described and characterized. See, for example, Rosner et al., Sex Hormone-Binding Globulin Mediates Steroid Hormone Signal Transduction at the Plasma Membrane, *J. Steroid Biochem. Mol. Biol.* Vol. 69:481-5 (1999); Petra, P.H. The plasma Sex Steroid Binding Protein (SBP or SHBG). A Critical Review of Recent Developments on the Structure, Molecular Biology, and Function, *J. Steroid Biochem. Mol. Biol.*, Vol. 40:735-53 (1991). A variety of methods have been used to quantify the serum concentrations of SHBG, including ammonium sulfate precipitation, gel filtration, equilibrium dialysis, dextran-coated charcoal, and radioimmunoassay. See, for example, Khan et al., Radioimmunoassay for Human Testosterone-Estradiol-Binding Globulin, *J. Clinical Endocrinology and Metabolism*, Vol. 54:705-710 (1982). Using a validated monoclonal immuno-radiometric assay (Endocrine Sciences, Calabassas

implant formulations are to be included in the term "non-oral," regardless of the physical location of implantation.

"Parenteral" administration can be achieved by injecting a drug composition intravenously, intra-arterially, intramuscularly, intrathecally, or subcutaneously, etc.

"Topical formulation" means a composition in which the drug may be placed for direct application to a skin surface and from which an effective amount of drug is released. Examples of topical formulations include but are not limited to ointments, creams, gels, transdermal patches, sprays, vaginal rings, and pastes. "Transdermal" refers to the route of administration that facilitates transfer of a drug through a skin surface wherein a transdermal composition is administered to the skin surface.

Transdermal administration can be accomplished by applying, pasting, rolling, attaching, pouring, pressing, rubbing, etc., of a transdermal preparation onto a skin surface. These and additional methods of administration are well-known in the art.

"Transdermal delivery system," "transdermal patches" or simply "patches" refer to a matrix or liquid reservoir type of delivery device which is used to transdermally deliver defined doses of a substance, over a specific application period.

One example of a transdermal patch for administering an androgenic steroid in accordance with this invention is a matrix-type patch which comprises an occlusive backing that is impermeable to the androgen steroids and defines the face or top surface of the patch and a solid or semisolid matrix layer comprised of a homogeneous blend of the hormone, a polymeric pressure sensitive adhesive carrier, and optionally one or more skin permeation enhancers. Matrix patches are known in the art of transdermal drug delivery. Examples without limitation, of adhesive matrix transdermal patches are those described or referred to in U.S. Patent Nos. 5,122,383 and 5,460,820 which are incorporated by reference in their entirety.

Another example of a transdermal patch for administering an androgenic steroid in accordance with this invention is a liquid reservoir system (LRS) type patch which comprises androgen, and other optional ingredients, such as a permeation enhancer, in a carrier vehicle. The carrier vehicle comprises a fluid of desired viscosity, such as a gel or ointment, which is formulated for confinement in a reservoir having an impermeable backing and a skin contacting permeable membrane,

as SHBG bind androgen or estrogen with high affinity to render them non-functional. One of skill in the art knows how to measure and characterize these types of bindings. See, for example Dunn et al.

Thus, the term "total testosterone serum level" refers to the sum of: (1) free testosterone; (2) testosterone which is weakly bound to serum proteins, such as albumin-bound testosterone; and (3) testosterone which is tightly bound bound to high affinity binding serum proteins, such as SHBG-bound testosterone.

The term "protein-bound" includes all types of protein bindings.

Total serum testosterone can be measured by known assay techniques such as a radioimmunoassay (RIA). See for example the RIA procedure used by Endocrine Sciences, Inc. (Calabassas Hills, CA). This procedure is based on the published RIA by Furuyama et al., Radioimmunoassay for Plasma Testosterone, *Steroids*. 1970;16:415-428. With this assay method, the normal range of total serum testosterone levels measured in healthy premenopausal women by Endocrine Sciences, Inc. was reported to be 14 to 54.3 ng/dL (Miller et al. 1998).

"Endogenous free testosterone level" or "physiological free testosterone level," shall refer to the free testosterone (FT) serum level that is normally found in adult women without symptoms associated with testosterone deficiency and/or testosterone excess, and/or imbalanced estrogen/androgen symptoms.

"Bioavailable", "serum bioavailable", and similar terms refer to androgen or estrogen that is not bound to SHBG. Therefore androgen which is "free" (unbound) or "weakly bound to" (easily dissociates from) serum albumin is considered to be bioavailable to tissues. Because of the high binding capacity (non-saturability) of albumin for testosterone, the serum concentration of albumin-bound testosterone will, in general, be proportional to the concentration of free testosterone. The proportionality factor corresponds to the product of the albumin-testosterone binding constant (3.6×10^4 L/mole) and the serum albumin concentration (expressed in mole/Liter). See, Vermeulen et al., A Critical Evaluation of Simple Methods for the Estimation of Free Testosterone in Serum, *J. of Clinical Endocrinology and Metabolism* Vol. 84:3666-3672 (1999). Since the concentration of serum albumin is maintained within a relatively narrow range (e.g. 4 – 5 g/dL; $5.8 \times 10^{-4} - 7.6 \times 10^{-4}$

retard changes in blood lipids which might otherwise predispose the woman to cardiovascular disease. In yet another aspect, the female may display a deficiency, or imbalance of estrogen and androgenic hormones. In yet another aspect, the female may be receiving oral estrogens for contraception.

"Improving health" refers to reducing, improving, or preventing the incidence and/or intensity of symptoms associated with androgenic steroid deficiency. Examples of such symptoms include but are not limited to: sexual dysfunction, which can manifest in loss of sexual desire, decreased sensitivity to sexual stimulation, decreased arousability and capacity for orgasm, diminished vital energy, depressed mood, diminished sense of well-being, increased shyness, loss of muscle mass and function, unfavorable body composition, i.e., lean to fat mass ratio, thinning and loss of pubic hair, urogenital atrophy, dry and brittle scalp hair, dry skin, decreased cognitive abilities, dry eyes, autoimmune phenomena, and a combination thereof.

Increases and decreases in the presence and severity of such symptoms may be ascertained through various devices known in the art for evaluating each particular symptom. For example, sexual function in women may be evaluated using self-assessment questionnaires, such as the Brief Index of Sexual Functioning for Women, (Taylor et al 1994); Derogatis Interview for Sexual Functioning, Derogatis, L., The Derogatis iInterview for Sexual Functioning (DISF/DISF-SR): an introductory report, *J. Sex. Marital Ther.* Winter 23(4):291-304 (1997); and other questionnaires, such as Derogatis et al., Psychological assessment measures of human sexual functioning in clinical Trials, *Int. J. Impot. Res.*, May 10 Suppl. 2:S13-20 (1998); as well as by genital blood flow methods (Laan 1998). Muscle mass, body composition and bone mineral density are commonly measured using dual energy x-ray absorptiometry (DEXA). Mood, well-being and neurocognitive function can be measured by the Beck Depression Inventory (Beck et al 1961), the Psychological General Well-being Index (Dupuy 1984), and a battery of neurocognitive function tests. Dry eye syndrome can be assessed by tear function tests, e.g., osmolality, volume, flow rate, Shirmer's test, by use of artificial tear preparations, and by subjective questionnaires. See, for example, Mathers et al. Menopause and Tear Function: The Influence of Prolactin and Sex Hormones on Human Tear Production, *Cornea* Vol. 17:353-8

Many evaluations may be employed for measuring the achievement of desired effects in the case of androgen and estrogen delivery, which are well known in the art. Such evaluations may be performed by a physician, or other qualified medical personnel, and may include physical examination, blood tests, etc.

"Therapeutic effect" refers to a desired result which is achieved to some degree. In the context of androgen and estrogen supplementation as presented in the present patent application, a number of desired results are referred to as "improving health." In one aspect, therapeutic effects may be achieved by delivering an "effective amount" of a substance capable of achieving the desired result to a selected degree. While the achievement of therapeutic effects may be measured by a physician or other qualified medical personnel using evaluations known in the art, it is recognized that individual variation and response to treatments may make the achievement of therapeutic effects a subjective decision.

Concentrations, amounts, solubilities, and other numerical data may be presented herein in a range format. It is to be understood that such range format is used merely for convenience and brevity and should be interpreted flexibly to include not only the numerical values explicitly recited as the limits of the range, but also to include all the individual numerical values or sub-ranges encompassed within that range as if each numerical value and sub-range is explicitly recited.

For example, a concentration range of 0.5 to 15 pg/ml should be interpreted to include not only the explicitly recited concentration limits of 0.5 pg/ml and 15 pg/ml, but also to include individual concentrations within that range, such as 0.5 pg/ml, 0.7 pg/ml, 1.0 pg/ml, 5.2 pg/ml, 11.6 pg/ml, 14.2 pg/ml, and sub-ranges such as 0.5-2.5 pg/ml, 4.8-7.2 pg/ml, 6-14.9 pg/ml, etc. This interpretation should apply regardless of the breadth of the range or the characteristic being described.

B. THE INVENTION

Recent research has shown that androgens, and particularly testosterone, contribute substantially to a woman's health and well-being. Ebert, et al., U.S. Patent 5,460,820, in one aspect, teaches a composition and method for administering testosterone transdermally via a patch delivery system. These compositions and

free testosterone levels, obtained before and during the second 3.5 day patch application period, were made by Endocrine Sciences. The resultant hormone data (mean ± SEM) for the three groups of surgically menopausal women participating in the clinical study is summarized in Table 2 below.

It should be noted that the normal range for SHBG levels is 36 to 185 nmol/L using the Endocrine Sciences assay. Further, changes in total testosterone and free testosterone levels represent the time-average changes from change from baseline levels during a 3.5 day patch application.

TABLE 2

Hormone (unit)	No ERT n=19	Transdermal E2 (0.1 mg/day) n=12	Oral CEE (1.25 mg/day) n=13
SHBG (nmol/L)	85.6 ± 9.6	90.8 ± 12.9	226.3 ± 13.5
Changes in Total T (ng/dl)	57.2 ± 4.4	53.6 ± 7.2	70.8 ± 9.6
Changes in Free T (pg/mL)	4.60 ± 0.40	4.20 ± 0.70	2.56 ± 0.30

In the above table:

E2 is estradiol
T is testosterone
CEE is conjugated equine estrogens

As shown in Table 2, the mean SHBG level in the oral estrogen group was approximately 2.5-fold larger than the other groups and exceeded the upper limit of the normal range. SHBG levels in the transdermal estrogen group were comparable to the women who did not receive estrogen replacement therapy (ERT). The mean increase in total serum testosterone levels during patch application, i.e. the time-averaged change from baseline, was approximately 30% greater in the oral estrogen group in comparison to the other two groups.

In contrast the mean increase in free serum testosterone level in the oral estrogen group was approximately 40% lower than in the other two groups. These

10	554	687	739	985	1313	1553	1656
15	831	1031	1108	1477	1969	2330	2484

For the delivery rates given above, the changes in total testosterone level (ng/dL) corresponding to a desired change in free testosterone level and a given SHBG level can be predicted using the power-law regression equation shown in Figure 1. Table 4 below provides an illustration of such predictions. As shown in Table 4, the changes in total testosterone level corresponding to a given change in free testosterone level increase markedly as the SHBG level increases. For example, the case corresponding to a change in free testosterone of 15 pg/mL in a patient whose SHBG level is 700 nmole/Liter (i.e. a delivery rate of 2484 mcg/day), the predicted increase in total testosterone is 820 ng/dL.

Table 4

SHBG (nmol/L):	**50**	**84**	**100**	**200**	**400**	**600**	**700**
Change in FT (pg/mL)	**Predicted Changes in Total Testosterone (ng/dL)**						
1	9	12	14	23	37	49	55
2.5	21	31	35	57	92	123	137
5	43	61	69	113	184	245	273
10	85	123	139	226	368	490	547
15	128	184	208	339	553	736	820

It should be appreciated that in extrapolating the findings and predictions of Tables 2, 3 and 4 to an actual patient, one must add the patient's baseline testosterone level (i.e. the level of total or free testosterone prior to treatment) to the expected change in testosterone level from the treatment. For individuals with baseline levels that are subnormal, the final hormone levels attained by treatment will be close to the change itself.

The above findings and predictions indicate that androgen administration to women on oral estrogens, or who have elevated SHBG levels in general, would produce free and/or bioavailable testosterone levels that would be significantly lower

pg/ml, or from about 2 to about 7 pg/ml. In yet another aspect of the invention, androgen may be administered at a dose sufficient to achieve a therapeutic effect equivalent to a free testosterone serum level of from about 3 to about 10 pg/ml.

In one aspect of the present invention, an androgen may be administered at a dosage sufficient to achieve a therapeutic effect equivalent to a bioavailable testosterone serum level of from about 1 to about 70 ng/dl. In another aspect of the present invention, an androgen may be administered at a dosage sufficient to achieve a therapeutic effect equivalent to a bioavailable testosterone serum level of from about 2 to about 35 ng/dl. In yet another aspect of the present invention, an androgen may be administered at a dosage sufficient to achieve a therapeutic effect equivalent to a bioavailable testosterone serum level of from about 2 to about 13 ng/dl.

In one aspect of the present invention, an androgen may be administered at a dosage sufficient to achieve a therapeutic effect equivalent to a total testosterone serum level of from about 15 to about 1000 ng/dl. In another aspect of the invention an androgen may be administered at a dosage sufficient to achieve a therapeutic effect equivalent to a total testosterone serum level of from about 85 to about 1000 ng/dl. In a further aspect of the invention, the androgen may be administered at a dosage sufficient to achieve a therapeutic effect equivalent to a total testosterone serum level of from about 100 to about 1000 ng/dl.

In one aspect of the invention, an androgen may be administered in a dosage sufficient to achieve a therapeutic effect equivalent to equivalent to a testosterone dosage of at least about 50 mcg/day. In another aspect, an androgen may be administered in a dosage sufficient to achieve a therapeutic effect equivalent to a testosterone dosage of from about 75 to about 3000 mcg/day. In a further aspect, an androgen may be administered at a dosage sufficient to achieve a therapeutic effect equivalent to a testosterone dosage of testosterone of from about 600 to about 3000 mcg/day. In yet another aspect, an androgen may be administered at a dosage sufficient to achieve a therapeutic effect equivalent to a testosterone dosage of testosterone of from about 700 mcg/day to about 3000 mcg/day.

One of the non-oral routes of delivery for an androgen dose is topical administration. Topical formulations may include a skin permeation enhancer(s) to

levels might even be within accepted physiological ranges but, based on other factors, for example, increased SHBG, sex hormone supplementation may still be appropriate.

Symptoms of subfunctional levels of androgens, including testosterone, might include, but not be limited to: sexual dysfunction, which can manifest in loss of sexual desire, decreased sensitivity to sexual stimulation, decreased arousability and capacity for orgasm; diminished vital energy; depressed mood; diminished sense of well-being; increased shyness; loss of muscle mass and function; unfavorable body composition, i.e., lean to fat mass ratio; thinning and loss of pubic hair; urogenital atrophy; dry and brittle scalp hair; dry skin; decreased cognitive abilities; dry eyes; autoimmune phenomena or exacerbation thereof, and a combination thereof.

Women who are receiving oral estrogens can also benefit from androgen therapy as it may reduce the breast tenderness that can occur with estrogen usage. Owing to known breast tissue anti-proliferative effects, androgens may also reduce the excess risk of breast cancer associated with estrogen use. It is therefore highly desirable, if not imperative, that testosterone supplementation for a female patient be based on a diagnosis by a physician who prescribes the mode of application, dosage and duration of treatment.

In so far as it is coadministered with androgenic steroids, estrogen, such as conjugated equine estrogen, may be administered orally in a dosage range of between about 0.2 to 3.0 mg/day. The dose may be adjusted according to an individual woman's needs and the potency of estrogen administered. The dose of oral estrogens can be taken in a single daily dose or in two or more smaller quantities. Ideally, for women who are experiencing vasomotor symptoms, the lowest effective dose of estrogen is used to control for vasomotor instability. Lower doses may be used in women who do not suffer vasomotor symptoms but will benefit from other health benefits, such as cardiovascular and bone benefits. In the case of oral contraceptive use, ethinyl estradiol is typically given cyclically in a 21 day on, 7 day placebo regimen.

In one aspect the present invention provides a method and kit for administering a progestin with androgen and estrogen. Progestins are known for administration to women to protect against endometrial hyperplasia. Progestins are

EXAMPLE 1

In surgically menopausal women between the ages of 20 and 55 years, oral estrogen and transdermal testosterone were administered as follows. The estrogen consisted of conjugated equine estrogen (Premarin® tablets) at a daily dose of 0.625 to 2.5 mg. The transdermal testosterone was administered by a matrix type transdermal patch that was applied to the abdomen twice weekly and has a delivery rate of 300 mcg/day. The duration of coadministration was 12 weeks. After 12 weeks, this regimen improved sexual function, mood and well-being in comparison to administration of conjugated equine estrogen alone.

Serum hormone levels measured on this regimen by Endrocrine Sciences (Calabassas Hills, CA) were found to be in the following ranges: total testosterone (15.5 to 254.3 ng/dL), free testosterone (1.7 to 33.7 pg/mL), bioavailable testosterone (2.3 to 71 ng/dl), estradiol (5 to 280 pg/mL), and estrone (8 to 410 pg/mL). Levels of sex hormone binding globulin ranged from 62.7 to 563 nmol/L with 92% being elevated and 48% being substantially elevated according to the definitions of "elevated," and "substantially elevated," provided herein. It is noteworthy that 73% of the women on the regimen of oral estrogen and transdermal testosterone achieved total testosterone levels in excess of 80 ng/dL, the upper limit of the normal range generally recognized in the art. In contrast, 78% had a free testosterone level below 6.8 pg/mL (the upper limit of the normal range for Endocrine Sciences), and 97% had a free testosterone level below 15 pg/mL, which is within the therapeutically acceptable range contemplated herein. Similarly, 68% of the women had a bioavailable tesosterone level below 12.7 ng/dL (the upper limit of the normal range for Endocrine Sciences), and 97% had a bioavailable testosterone level below 35 ng/dL, which is within the therapeutically acceptable range contemplated herein.

EXAMPLE 2

A combination of an androgenic compound and an estrogenic compound may be administered to women who are naturally menopausal according the following regimen:

Androgen: topical administration of testosterone in an appropriate carrier vehicle, such as a cream or ointment, that optionally contains a permeation enhancer

in sesame oil. In order to provide 150 mg of testosterone enanthate, the injected dose is 0.75 mL.

Estrogen: oral estrogens are given in a range of 0.3 to 3.0 mg/day.

Administration is performed as long as benefits of treatment are desired and deemed appropriate by a prescribing physician.

EXAMPLE 4

An androgenic compound and an estrogenic compound may be administered to women with premature ovarian failure, e.g., women whose ovarian function permanently ceases prior to age 40.

Androgen: methyltestosterone may be delivered via the buccal route at a dose of 1 mg/day to achieve an improvement in sexual function that is equally efficacious to an improvement produced by testosterone at serum levels of about 50 to 300 ng/dL. The buccal tablet may be a bilayer tablet consisting of a drug layer and a bio-adhesive layer (both 50 mg each). The composition of the drug layer (in weight percent) may be 2% methyltestosterone, 0.75 % magnesium stearate, 0.1% FD&C yellow #6, 24% Klucel HXF, and 73.15% mannitol. The composition of the bio-adhesive layer (in weight percent) may be 69.25% polyethylene oxide, 30% carbomer 934P, and 0.75% magnesium stearate. The adhesive side of the tablet is affixed to the gingiva of the upper jaw and the drug side of the tablet faces the overlying buccal mucosa. Drug is absorbed transmucosally as the tablet dissolves over time. The tablet may be applied once daily after breakfast.

Estrogen: Estrace®, Bristol-Myers Squibb Co., an oral micronized estradiol product in tablet form, may be administered at a dosage of 2 mg/day to alleviate menopausal symptoms and prevent bone loss.

In addition a progestin, such as medroxyprogesterone acetate, may be orally administered at a dose of 5 mg/day for the last ten days of each month to induce endometrial sloughing.

While the examples have been directed primarily to the delivery of an androgenic steroid to provide needed supplementation based on determination of a

Claims

What is claimed is:

1. A kit for improving the health of a woman having an elevated, or substantially elevated level of sex hormone binding globulin (SHBG), comprising a non-oral dosage form of an androgenic steroid, in an amount sufficient to provide a therapeutic effect in the presence of elevated or substantially elevated SHBG levels.

2. The kit of claim 1, wherein said androgenic steroid is a member selected from the group consisting of: testosterone, methyltestosterone, androstenedione, adrenosterone, dehydroepiandrosterone, oxymetholone, fluoxymesterone, methandrostenolone, testolactone, pregnenolone, 17α-methylnortestosterone, norethandrolone, dihydrotestosterone, danazol, oxymetholone, androsterone, nandrolone, stanozolol, ethylestrenol, oxandrolone, bolasterone and mesterolone, testosterone propionate, testosterone cypionate, testosterone phenylacetate, testosterone enanthate, testosterone acetate, testosterone buciclate, testosterone heptanoate, testosterone decanoate, testosterone caprate, testosterone isocaprate, isomers and derivatives thereof, and a combination thereof.

3. The kit of claim 1, wherein said androgenic steroid is present in a non-oral dosage form sufficient to achieve a therapeutic effect equivalent to a total testosterone serum level of from about 15 to about 1000 ng/dl.

4. The kit of claim 1, wherein said androgenic steroid is present in a non-oral dosage form sufficient to achieve a therapeutic effect equivalent to a free testosterone serum level of from about 0.5 to about 30 pg/ml.

5. The kit of claim 1, wherein said androgenic steroid is present in a non-oral dosage form sufficient to achieve a therapeutic effect equivalent to a bioavailable testosterone serum level of from about 1 to about 70 ng/dl.

14. Use of an androgenic steriod for the manufacture of a medicament which, when administered non-orally in an effective amount, improves the health of a woman having an elevated or substantially elevated level of sex hormone binding globulin (SHBG).

15. The use according to claim 14, wherein said elevated SHBG level is above about 84 nmole/L.

16. The use according to claim 14, wherein said substantially elevated SHBG level is above about 185 nmole/L.

17. The use according to claim 14, wherein said substantially elevated SHBG level is above about 300 nmole/L.

18. The use according to any one of claims 14-17, wherein the woman is receiving orally administered estrogen supplementation.

19. The use according to claim 18, wherein the orally administered estrogen supplementation is co-administered with the non-orally administered androgenic steroid.

20. The use according to claims 18 or 19, wherein said orally administered estrogen is a member selected from the group consisting of: 17β-estradiol, 17α-estradiol, conjugated equine estrogen, esterified estrogen, micronized estradiol, sodium estrogen sulfate, ethinyl estradiol, estrone, tibolone, selective estrogen receptor modulator (SERM), phytoestrogen, isomers and derivatives thereof, and a combination thereof.

phenylacetate, testosterone enanthate, testosterone acetate, testosterone buciclate, testosterone heptanoate, testosterone decanoate, testosterone caprate, testosterone isocaprate, isomers and derivatives thereof, and a combination thereof.

27. The use according to any one of claims 14-26, wherein said androgenic steroid is administered in a dosage sufficient to achieve a therapeutic effect equivalent to a total testosterone serum level of from about 15 to about 1000 ng/dl.

28. The use according to claim 27, wherein said androgenic steroid dosage is sufficient to achieve a therapeutic effect equivalent to a total testosterone serum level of from about 85 to about 1000 ng/dl.

29. The use according to claim 27, wherein said androgenic steroid dosage is sufficient to achieve a therapeutic effect equivalent to a total testosterone serum level of from about 100 to about 1000 ng/dl.

30. The use according to any of claims 14-26, wherein said androgenic steroid is administered in a dosage sufficient to achieve a therapeutic effect equivalent to a free testosterone serum level of from about 0.5 to about 30 pg/ml.

31. The use according to claim 30, wherein said androgenic steroid dosage is sufficient to achieve a therapeutic effect equivalent to a free testosterone serum level of from about 1 to about 15 pg/mL.

32. The use according to claim 30, wherein said androgenic steroid dosage is sufficient to achieve a therapeutic effect equivalent to a free testosterone serum level of from about 3 to about 10 pg/ml.

40. The use according to claim 37, wherein said androgenic steroid is administered in a dosage sufficient to achieve a therapeutic effect equivalent to a testosterone dosage of from about 700 to about 3000 mcg/day.

41. The use according to any one of claims 14-40, wherein said non-oral administration is topical administration, or parenteral administration, or a combination thereof.

42. The use according to claim 41, wherein said parenteral administration is intramuscular injection, or subcutaneous implantation, or a combination thereof.

43. The use according to claim 41, wherein said topical administration is transdermal, transmucosal, or sublingual, or a combination thereof.

44. A method of improving health in a woman having elevated or substantially elevated sex hormone binding globulin (SHBG) levels, comprising administering a medicament as in any one of claims 14-43.

21. The use according to claims 18, wherein said estrogen is administered in a dosage sufficient to achieve a therapeutic effect equivalent to a conjugated equine estrogen dosage of from about 0.2 to about 3.0 mg/day.

22. The use according to any one of claims 18, further wherein the woman is also being treated with progestin.

23. The use according to claim 22, wherein said amount of progestin is sufficient to provide endometrial safety.

24. The use acccording to claim 22, wherein said amount of progestin is sufficient to provide effective contraception.

25. The use according to claim 14, wherein said improvement in the health of a woman, is manifested by restoration, enhancement, or improvement of a characteristic selected from the group consisting of: sexual desire, stimulation to sexual organs, ability to achieve orgasm, pleasure in sexual activity, increase in sexual activity, vital energy, sense of well-being, mood and sense of emotional well being, shyness, cognitive abilities, muscle mass and function, body composition, bone mineral density, skin and hair condition, pubic hair, urogenital atrophy, vaginal dryness, dry eyes, health in autoimmune conditions, vasomotor instability, breast tenderness, symptoms of premenstrual syndrome, and a combination thereof.

26. The use according to claim 14, wherein said androgenic steroid is a member selected from the group consisting of: testosterone, methyltestosterone, androstenedione, adrenosterone, dehydroepiandrosterone, oxymetholone, fluoxymesterone, methandrostenolone, testolactone, pregnenolone, 17α-methylnortestosterone, norethandrolone, dihydrotestosterone, danazol, oxymetholone, androsterone, nandrolone, stanozolol, ethylestrenol, oxandrolone, bolasterone and mesterolone, testosterone propionate, testosterone cypionate, testosterone

33. The use according to claim 30, wherein said androgenic steroid dosage is sufficient to achieve a therapeutic effect equivalent to a free testosterone serum level of from about 2 to about 13 pg/ml.

34. The use according to claim 14, wherein said androgenic steroid is administered in a dosage sufficient to achieve a therapeutic effect equivalent to a bioavailable testosterone serum level of from about 1 to about 70 ng/dl.

35. The use according to claim 34, wherein said androgenic steroid dosage is sufficient to achieve a therapeutic effect equivalent to a bioavailable testosterone serum level of from about 2 to about 35 ng/dl.

36. The use according to claim 34, wherein said androgenic steroid dosage is sufficient to achieve a therapeutic effect equivalent to a bioavailable testosterone serum level of from about 2 to about 13 ng/dl.

37. The use according to claim 14, wherein said androgenic steroid is administered in a dosage sufficient to achieve a therapeutic effect equivalent to a testosterone dosage of at least about 50 mcg/day.

38. The use according to claim 37, wherein said androgenic steroid is administered in a dosage sufficient to achieve a therapeutic effect equivalent to a testosterone dosage of from about 75 to about 3000 mcg/day.

39. The use according to claim 37, wherein said androgenic steroid is administered in a dosage sufficient to achieve a therapeutic effect equivalent to a testosterone dosage of from about 600 to about 3000 mcg/day.

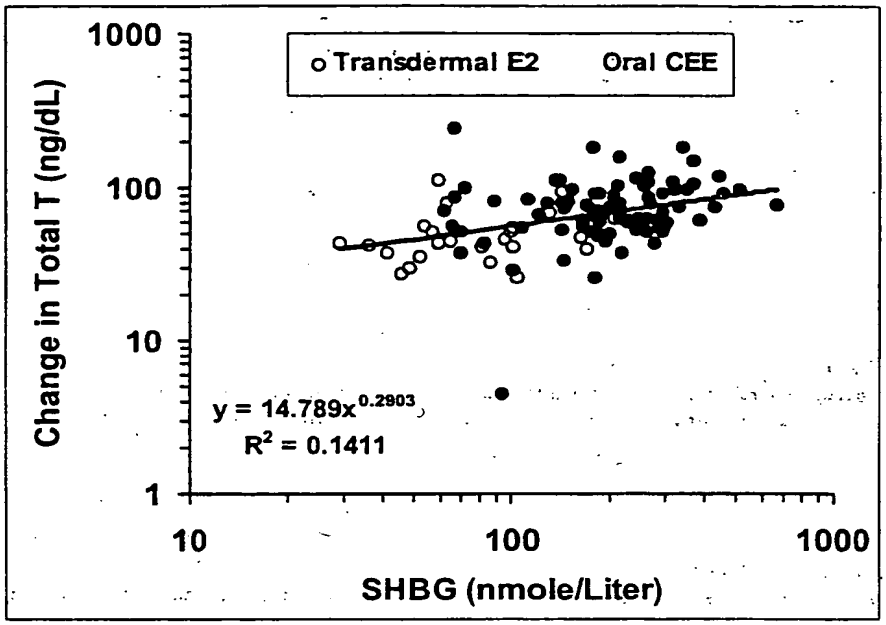


Figure 1

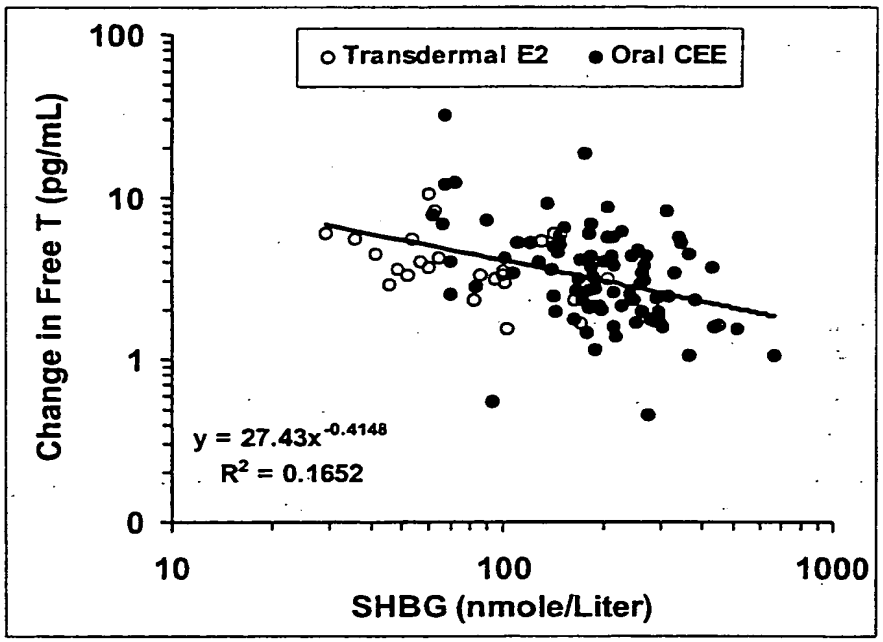


Figure 2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/15834

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 20-44
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.